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Award Number: W81XWH-12-1-0216

TITLE: Targeting Histone Demethylase GASC1/JMJD2C/KDM4C as a Novel Therapeutic Strategy in Castration-Resistant Prostate Cancer

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REPORT DATE: September 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2013	Annual	1 September 2012 – 31 August 2013

4. TITLE AND SUBTITLE

Targeting Histone Demethylase GASC1/JMJD2C/KDM4C as a Novel Therapeutic Strategy in Castration-Resistant Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-12-1-0216

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Wayne State University
Detroit, MI 48201

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Prostate cancer is the most common malignancy amongst men worldwide and stands as the second leading cause of cancer deaths. The goal of this study was to assess the therapeutic potential of selective inhibitors for the oncogenic lysine-specific demethylase 4C (KDM4C, also known as GASC1 and JMJD2C) in highly lethal, metastatic castration-resistant prostate cancer (CRPC), for which effective treatments are urgently needed. The GASC1 gene, originally cloned from an amplified region at 9p24 in esophageal cancer cells, is over-expressed in a diverse array of human cancers, including prostate cancer in which it correlates with a poor prognosis for these patients. We found that GASC1 is overexpressed at both the mRNA and protein levels in metastatic CRPCs, and that knockdown of GASC1 inhibits proliferation of CRPC cells in vitro. The GASC1 demethylase plays an essential role in affecting chromatin architecture and gene expression; furthermore, it physically associates with the androgen receptor (AR), a key effector of the survival and growth of CRPCs. Knocking down GASC1 significantly reduced expression of a set of classical and CRPC-specific AR target genes in CRPC cells. Importantly, targeting histone demethylases is an active frontier in epigenetic drug development. Our data indicates that targeting the GASC1 demethylase is a promising strategy to control CRPC or prevent its emergence.

15. SUBJECT TERMS
Prostate Cancer, CRPC, Histone Demethylase

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

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Introduction

Prostate cancer is the most common malignancy among men worldwide and it is the second leading cause of cancer related deaths. Early-stage prostate cancers can be managed by various treatments, including a hormone (androgen)-depletion therapy. Although the cancer is temporarily manageable by hormone deprivation, it often stops responding to this therapy. When this event occurs, the disease is now called castration-resistant prostate cancer, CRPC. Paradoxically, most of these CRPCs continue to express the androgen receptor (AR) and remain dependent on AR signaling for growth and proliferation. Previously, our group originally identified and cloned the GASC1 (gene amplified in squamous cell carcinoma 1, also known as KDM4C and JMJD2C) gene from an amplified region at 9p24 in esophageal cancer cells; and demonstrated that GASC1 is amplified and over-expressed in various tumor types. Recently, the GASC1 (KDM4C) protein has been identified as a member of the KDM4 family of histone demethylases. The Jumonji domains of the KDM4 family mainly catalyze the demethylation of tri- and di-methylated histone 3 lysine 9 (H3K9me3/me2) and lysine 36 (H3K36me3/me2) marks, thus regulating chromatin structure and gene expression. Importantly, GASC1 interacts directly with the AR and works as an essential coactivator of AR-induced transcription and cellular growth (1, 2). Furthermore, accumulated evidence indicates that epigenetic programming via histone methylation plays a critical role at every stage of prostate tumorigenesis. However, the pathological role that GASC1 histone demethylases play in prostate cancer, particularly in CRPC, remains unclear. In this research project, we hypothesized that up-regulation of GASC1 promotes CRPC progression by facilitating AR transcriptional activity through epigenetic histone modulations. Thus, suppressing GASC1 will reprogram AR-mediated signaling pathways and reverse the castration-resistant phenotype of prostate cancer.

Body

1. Specific Aims

This project consists of two specific aims:
Aim 1: To investigate the role of GASC1 in promoting the castration-resistant phenotype of prostate cancer and examine the potential of GASC1 as a therapeutic target in CRPCs.
Aim 2: To determine how GASC1 facilitates AR transcriptional activity in CRPC by examining how GASC1 affects AR target genes and their associated histone methylation status.

2. Studies and Results

Task 1: To investigate the role of GASC1 in promoting the castration-resistant phenotype of prostate cancer and examine the potential of GASC1 as a therapeutic target in CRPCs.

In 2000, we originally cloned the *GASC1* gene from a poorly differentiated, aggressive esophageal cancer cell line by using a positional cloning strategy (3). Recent studies from our lab and others indicate that GASC1 is upregulated in various human tumors; this upregulation correlates with a poor prognosis for cancer patients (4-12). For example, we demonstrated that the GASC1 gene is amplified and over-expressed in approximately 15% of breast cancers; its amplification/overexpression is more prevalent in the basal breast cancer subtype, which is particularly aggressive and accounts for a disproportionate number of breast cancer deaths (7, 13). To determine the expression pattern and role of GASC1 in prostate cancer, we first examined the expression of GASC1 in a panel of normal and cancerous prostate epithelial cell lines using quantitative RT-PCR and Western blot assays. We found that prostate cancer cells, particularly CRPC (CWR22Rv1 and C4-2B), express much higher levels of GASC1 than the nonmalignant cells (Figure 1). Next, we conducted a large-scale meta-analysis monitoring altered GASC1 mRNA gene expression across multiple available gene expression studies. We found that GASC1 is highly expressed in prostate carcinoma tissues compared with normal prostate tissues in several independent studies. More importantly, GASC1

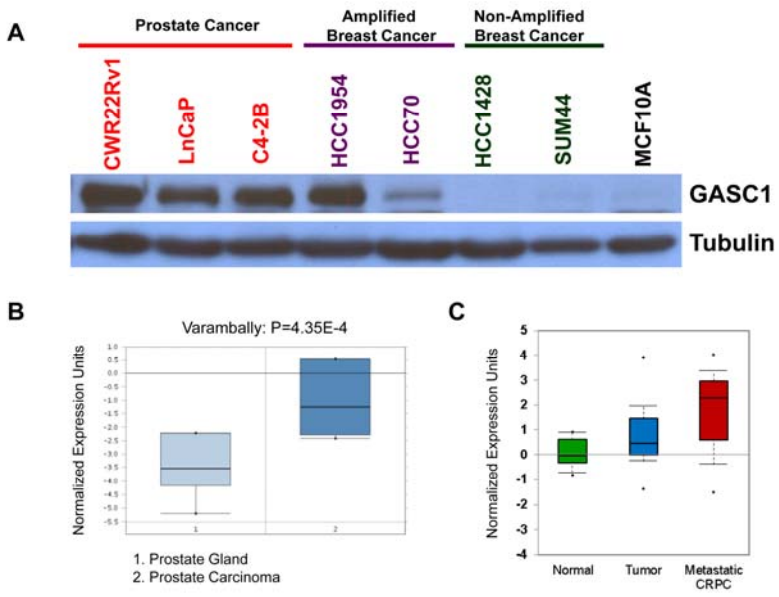

Figure 1. GASC1 is over-expressed in prostate cancer, particularly in CRPCs. (A) GASC1 protein levels in a panel of breast and prostate cancer lines were determined by Western blot. A nontumorigenic epithelial MCF10A cell line was used as the control. (B) A published study shows GASC1 transcript expression in prostate cancers based on Oncomine analysis. (C) GASC1 is highly expressed in metastatic CRPCs based on Grasso's study ($P<0.001$).

is significantly over-expressed in metastatic CRPCs, implying it plays important roles in promoting CRPC progression (14).

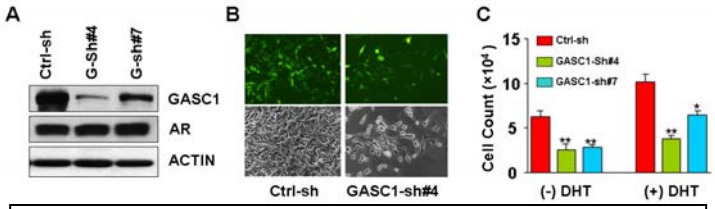

Figure 2. (A) C4-2B cells were infected with non-silencing control pGIPZ-shRNA (Ctrl-sh) or pGIPZ-GASC1 shRNA #4 and #7 (G-sh#4 and #7). Western blot showed GASC1 and AR protein levels in stable shRNA knockdown cells and control cells. (B) shRNA-mediated knockdown of GASC1 in C4-2B cells inhibits cell growth under standard culture conditions. (C) GASC1 knockdown inhibited C4-2B cell growth under conditions of hormone starvation in the presence or absence of DHT for 1 week (* P<0.05 and ** P<0.01, Student's t test).

Given that GASC1 is over-expressed in CRPC cells, we next used an shRNA approach to explore whether GASC1 knockdown would affect the proliferation and aggressive cancer phenotypes of CRPC cells. To perform knockdown experiments, we obtained seven pGIPZ-GASC1 shRNA expression constructs from OpenBiosystems (http://www.openbiosystems.com/). In this pGIPZ vector, TurboGFP and shRNA are part of a single transcript that visually marks the shRNA-expressing cells. We identified the two most efficient pGIPZ-shRNAs that knock down GASC1 expression levels in tumor cells (Figure 2A). No significant change in the expression of other KDM4 family members, as well as the AR protein, was detected in GASC1-shRNA knockdown cells, thus ruling out possible off-target effects of GASC1-shRNAs (Figure 2A). GASC1 knockdown dramatically slowed cell growth of C4-2B CRPC cells under standard culture conditions (10% FBS) (Figure 2B). Next, we analyzed the growth of GASC1 knocked down C4-2B cells under conditions of hormone starvation (10% charcoal-stripped FBS) with or without dihydrotestosterone (DHT, 10 nM) treatment. Our preliminary results revealed that GASC1 knockdown inhibited cell growth in the presence or absence of DHT. The results were most striking under conditions of hormone starvation, in which GASC1 knockdown inhibited cell proliferation by ~60% (Figure 2C). We further extended our studies to another CRPC model cell line, CWR22Rv1, which expresses both full-length AR and a constitutively active, truncated AR lacking the ligand-binding domain (LBD).(15) We found that knocking down GASC1 also significantly inhibits CWR22Rv1 cell growth and colony formation under standard culture conditions (Figure 3). Taken together, shRNA knockdown experiments indicate that inhibiting GASC1 has the potential to block prolifieration in CRPC cells.

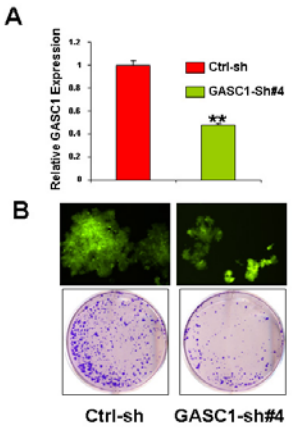

Figure 3. (A) qRT-PCR showed GASC1 mRNA levels in CWR22Rv1 cells after infection with non-silencing control pGIPZ-shRNA (Ctrl-sh) or pGIPZ-GASC1 shRNA #4. The baseline for the control-shRNA cells was arbitrarily set as 1. (** P<0.01). (B) shRNA-mediated knockdown of GASC1 in CWR22Rv1 cells inhibits cell growth and colony formation under standard culture conditions.

<u>Task 2: To determine how GASC1 facilitates AR transcriptional activity in CRPC by examining how GASC1 affects AR target genes and their associated histone methylation status.</u>

Previous studies revealed that the GASC1 protein interacts with the AR and functions as a co-activator of AR-induced transcription in LNCaP cells (2). We performed immunoprecipitation (IP) assays that validated the interaction between GASC1 and the AR in C4-2B cells under conditions of hormone starvation (Figure 4). Recently, a subset of AR target genes that control cell division was shown to be selectively upregulated in CRPC cells regardless of ligand. These CRPC-specific AR targets include UBE2C, CDC20, CDK1, CCNA2, and others (16). To explore the contribution of GASC1 to endogenous AR-regulated gene expression in C4-2B cells, we performed quantitative RT-PCR (qRT-PCR) assays to measure the expression of both classical AR target genes (including PSA/KLK3, KLK2, FKBP5, and NDRG1) and CRPC-specific genes (including UBE2C, CDK1, CDC20, and CCNA2) in C4-2B cells with or without GASC1 knockdown. We found that knocking down GASC1 significantly reduced transcript levels of a set of classical and CRPC-specific AR target genes in either the presence or absence of DHT (Figure 5). Since GASC1 is the key histone demethylase that is constitutively associated with the AR and specifically erases tri- and dimethylated H3K9 repressive marks(1, 2, 17, 18), it is plausible that GASC1 regulates AR transcriptional activity and specificity by directly modifying the histone lysine methylation status of CRPC-specific target genes, including cell cycle genes.

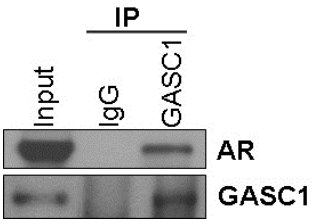

Figure 4. GASC1 protein co-immunoprecipreciptes with AR in C4-2B cells under conditions of hormone starvation.

To address how GASC1 overexpression alters the histone methylation code and affects the transcription of target genes implicated in human prostate cancer, we then sought to determine the GASC1 binding sites across the human genome and identify the direct targets of GASC1 by a chromatin immunoprecipitation combined with high throughput sequencing (ChIP-Seq) approach in prostate cancer. We successfully transduced V5-tagged wild-type GASC1 into LNCaP cells, and then performed ChIP-seq assays in these LNCaP-GASC1 cells by using V5 ChIP-grade antibody. We identified 12,570 ChIP peaks, and most GASC1 binding peaks (10433, 83.00%) were found at gene promoters [herein defined as -7500/+2500 bp of the TSS] and that 8850 peaks (70.41%) were localized between -500 and +500 bp relative to the TSSs. Pathway Analysis revealed that GASC1-bound genes were significantly associated with several important biological functions, including cell cycle and cancer pathways.

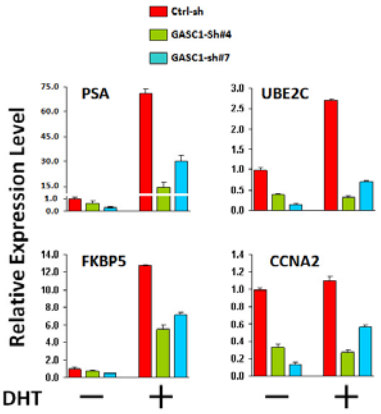

Figure 5. Knocking down GASC1 impairs the expression of both classical and CRPC-specific AR target genes. qRT-PCR assays show expression levels of both classical AR target genes (PSA/KLK3 and FKBP5), and CRPC-specific AR target genes (UBE2C and CCNA2) in GASC1 knocked down (GASC1-sh#4 and #7) C4-2B cells or control (Ctrl-sh) C4-2B cells under conditions of hormone starvation with or without 10 nM DHT treatment for 24 hours.

Remaining work for no-cost extension: It is necessary to validate the ChIP-seq data with the ChIP-PCR method in prostate cancer cells. We need to examine the correlation between GASC1 binding and histone H3K9 and H3K36 methylation marks at genomic regions of these GASC1 target genes in prostate cancer cells. In addition, we need to further examine the effect of GASC1 demethylation function on castration-resistant and aggressive transforming phenotypes of prostate cancer cells.

Key Research Accomplishments

The highlights of our accomplishments from the past year are: (1) we demonstrated that GASC1 is highly expressed in prostate cancer, particularly in CRPCs; (2) we stably knocked down or over-expressed GASC1 in various prostate model cells utilizing lentiviral-based shRNA or over-expression systems; (3) we found that knocking down GASC1 inhibits cell growth and *in vitro* aggressive cancer phenotypes in CRPC lines: C4-2B and CWR22Rv1; (4) we determined genome-wide GASC1 binding sites with the ChIP-Seq approach in LNCaP-GASC1 prostate cancer model cells; and (5) we found that GASC1 has potential to modulate expression of a set of classical and CRPC-specific AR target genes in CRPC cells.

Reportable Outcomes

Abstracts:

1. Zhang L, Hou JL, Holowatyj A and **Yang Z-Q.** The role of histone demethylase GASC1 in promoting prostate cancer progression. 104st American Association for Cancer Research Annual Meeting in Washington, DC, Apr 4-10, 2013 (see Appendix)
2. **Yang Z-Q**. The role of histone demethylase GASC1 in cancer and its therapeutic potential. COLD SPRING HARBOR ASIA: DifferentiationTherapy and Advances in Cancer, Suzhou, China. October 20-24, 2012 (Selected for the oral presentation)

Conclusion

We have made significant progress in the past year in characterizing the histone lysine demethylase, GASC1, in human prostate cancer. We found that GASC1 is over-expressed in prostate cancer, particularly in CRPCs. We established a series of prostate model cells that stably knocked down or over expressed GASC1 proteins. We demonstrated that knocking down GASC1 inhibits cell growth and *in vitro* aggressive cancer phenotypes in CRPC cells. Furthermore, we determined genome-wide GASC1 binding sites with the ChIP-Seq approach in LNCaP prostate cancer cells. We revealed that most GASC1 binding peaks (83.00%) were found at gene promoters in prostate cancer, implying it plays an important role in regulating gene expression.

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Control/Tracking Number: 13-A-3136-AACR
Activity: Abstract Submission
Current Date/Time: 11/14/2012 5:52:41 PM

The role of histone demethylase GASC1 in promoting prostate cancer progression

Short Title:
GASC1 in prostate cancer

Author Block: Lihong Zhang, Jinling Hou, Andreana Holowatyj, Zeng-Quan Yang. Barbara Ann Karmanos Cancer Inst., Detroit, MI

Abstract:
Prostate cancer affects 1 in 6 American men, and is the second leading cause of cancer-related deaths in males. The defiance of castration-resistant prostate cancer (CRPC) to currently available treatments represents the most challenging aspect of this disease. Although resistant to androgen deprivation treatment, most CRPCs continue to express the androgen receptor (AR) and remain dependent on AR signaling for growth and proliferation. Previously, we cloned a novel gene, GASC1 (gene amplified in squamous cell carcinoma 1), from 9p24 amplified cancer cells. Recently, the GASC1 protein has been identified as a key histone demethylase that controls chromatin-mediated regulation of gene expression. Importantly, the GASC1 protein interacts with the AR and serves as a co-activator of AR-induced transcription in prostate cells. In this study, we demonstrated that various aggressive tumors, including CRPCs, have upregulated GASC1. We used an shRNA approach to determine whether GASC1 knockdown would affect the proliferation and transformation of CRPC cell lines. We found that knocking down GASC1 inhibits growth and colony formation of CRPC cells (C4-2B and CWR22Rv1) in vitro. Previously, it was reported that the GASC1 protein interacts with the AR and functions as a co-activator of AR-induced transcription in LNCaP cells. The GASC1 protein contains N-terminal Jumonji catalytic domains and C-terminal Tudor and PHD domains; however, which domains are responsible for the association of GASC1 with the AR have not yet been identified. To address this question, we generated stable LNCaP cell lines expressing V5-tagged N-terminal Jumonji catalytic domains and C-Terminal PHD/Tudor domains, and performed Co-IP analyses. We found that the C-terminal region is essential for GASC1 association with the AR in prostate cancer cells. To explore the contribution of GASC1 to endogenous AR-regulated gene expression in AR-positive CRPC cells, we performed quantitative RT-PCR assays to measure the expression of both classical AR target genes (including PSA/KLK3, KLK2, FKBP5, and NDRG1) and CRPC-specific genes (including UBE2C, CDK1, CDC20, and CCNA2) in C4-2B cells with or without GASC1 knockdown. We found that knocking down GASC1 significantly reduced transcript levels of a set of classical and CRPC-specific AR target genes in either the presence or absence of the AR ligand. Our data demonstrates that GASC1 is a target of substantial relevance to aggressive prostate cancers, including CRPCs. As such, targeting GASC1 is a promising strategy to control CRPC or prevent its emergence.
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Author Disclosure Information: L. Zhang: None. J. Hou: None. A. Holowatyj: None. Z. Yang: None.
Sponsor (Complete):
Category and Subclass (Complete): MCB04-04 Nuclear oncoproteins and tumor suppressor genes
Research Type (Complete): Basic research
Keywords/Indexing (Complete): Histone modification ; Oncogene ; Prostate cancer ; Androgen receptor
Submission Details (Complete):
*Primary Organ Site: Not Applicable
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